

Treatment of Tuberculosis

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THE INTRODUCTION of streptomycin into the clinical treatment of tuberculosis in 1944 and the subsequent use of other drugs have led to radical changes in the management of this disease. Indeed, there has been no other comparable period in its history. The momentum originally imparted by the discovery of antituberculosis drugs is still felt, and it would be rash to predict when or where it may spend itself, so swift is the rush of events. It seems prudent, therefore, to characterize the following remarks as more of a commentary than a critique.

In the relatively short time since tuberculous patients first received streptomycin, it has been found possible, by adjusting the dosage and combining its administration with that of para-aminosalicylic acid, to circumvent most of its serious toxic properties, as well as to prolong the antimycobacterial effect through many more months than either drug would accomplish alone. There are now a number of other active

antituberculosis drugs, the most potent of which are isoniazid and viomycin. Consequently, the variety of drug combinations which may be used simultaneously and in sequence becomes large and the task of assessing their efficacy quite formidable.

An accurate evaluation can be arrived at only after patient and sustained efforts in the laboratory and clinic, which will require years. Eagerness for progress should not be permitted to disrupt the methodical, time-consuming pursuit of scientific facts upon which clinical practice ultimately must stand. In dealing with a problem as complex as tuberculosis, a get-wise-quick approach is thoroughly unsound.

Early Favorable Effects

Largely because of the use of specific drugs, the early response of the tuberculous patient to treatment can now be said to be more uniformly favorable, more certainly predictable and, on the average, more rapid than ever before. Whatever the regimen adopted, the first maneuver in treatment is to attempt, as rapidly as possible, to suppress the activity of the tubercle bacillus and thus halt active, progressive disease. The effect of successful treatment is manifested by an abatement of toxemia—allowing the patient to recover his strength and feeling of well-being—and by a gradual restoration of normal physiological processes. Another easily observed effect is the retardation or arrest of active inflammation and destruction of tissue.

The early favorable effects of treatment are often conspicuous. The cough and expectoration may disappear, and drainage from discharging sinuses may dry up completely. The

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subsidence of inflammation may also be followed by a resolution and absorption of inflammatory products which is remarkable or even dramatic. All this may be observed in the space of 3 or 4 months. But then further regressive changes of the lesions often tend to occur more slowly, and a time may come, perhaps after many more months, when little or no further change is observed, even though the symptomatic recovery is maintained.

Although the early halting of active inflammation and of exudation in and discharge from tuberculous lesions may not be synonymous with the death of the bacteria responsible, these favorable changes nevertheless benefit the patient. At the peak of these effects, necrotic lesions sometimes can be removed surgically without great operative risk. Therefore, one may think of the drying out of lesions as one of the most beneficent, rapid, and striking effects of specific drugs.

Drug Therapy vs. Rest Treatment

The mechanisms of healing under the influence of specific drugs do not appear to be essentially different from those occurring under natural conditions, often favored by a regimen of rest. With minor exceptions, the difference in the early response to treatment does not seem to be qualitative but, rather, a matter of speed and predictability. Thus, the question is raised as to whether these new developments justify or necessitate a change in our ideas regarding the use of rest treatment, which long experience has proved so helpful against tuberculosis.

An answer is difficult because of our limited knowledge of the way in which rest treatment exerts its favorable effects. These effects are vaguely identified as biochemical, hormonal, and general, but not primarily mechanical. Innate factors seem to be vital, and there is reasonable assurance that in most patients these can be raised to better levels by rest treatment and other general measures. If this be so, can specific drug therapy in any way substitute for rest? Certainly, during the early phases of active, progressive tuberculosis, when resistance is low, it seems rational and obligatory to give the patient the benefit of every

available help. It is rather generally agreed, therefore, that rest treatment and general adjuvants are just as important as the administration of drugs, and in many cases probably more so.

Measuring Resistance

Since there is no accurate objective measure of resistance, it is necessary to estimate it almost entirely by clinical judgment based on experience. Although the early response to drug therapy is in most cases consistently favorable, the tendency to relapse after the discontinuance of therapy varies widely in different patients, and this tendency almost certainly is related in part to the level to which resistance has risen. It is much easier, therefore, to identify the time and circumstances initially calling for drugs than it is to identify the time to stop them. In some patients, an early relapse indicates that chemotherapy has been stopped prematurely; in others, it is continued for an unnecessarily long time, ostensibly for safety's sake.

This dilemma illustrates the practical problem of the physician and his patient, who perforce cannot wait for the laboratory to produce a reliable test of resistance. The best test we have now is the tolerance of the patient for gradually increasing activity, especially physical exercise. And since resistance is the only permanent defense against the infection, it is logical to stop chemotherapy (at a time when healing of the disease is judged to be well advanced) before allowing the patient unrestricted activity, and then gradually to test his tolerance of greater liberty under carefully observed conditions. Justification may be found for speeding his return to a productive life or to more prolonged and radical treatment. This is another one of the problems which require long and careful study.

Condition of Tubercle Bacilli

A word should be said about the condition of the tubercle bacilli which remain in tuberculous lesions, particularly those of a solid necrotic character, after the patient has recovered and his disease is called arrested or inactive. It

has long been recognized, on the one hand, that the bacteria may survive there for many decades while the patient remains well. Should a relapse occur, these survivors or their descendants are usually found to be the culprits. On the other hand, the bacteria may eventually disappear from the lesions or, if persisting, they may be found incapable of growth on artificial culture media or of causing disease in susceptible animals. A very lively question at the moment is whether the remaining bacilli are really dead, leaving behind only their skeletal remains, or whether they have merely been so enfeebled and modified by the antagonistic forces of nature that they are unable to keep their tenuous hold on life except in the lesions in which they are found.

How long is required under natural conditions for such changes to occur is largely conjectural, but usually it seems to be a matter of many years. It now appears that the continuous administration during many months of combinations of specific drugs such as streptomycin and para-aminosalicylic acid sometimes exerts similar effects on the bacteria. This observation tempts the most critical scientist to entertain the thought that the bacteria may have been killed by the drugs. It is legitimate to pursue the thought and this is being done in various laboratories. Meanwhile, it seems wise and sound to take the position that sterilization of lesions by drugs has not been proved.

Treatment Principles

In sum, it may be said that even though the patient profits greatly from the use of specific drugs when they are needed and may experience an early halting of serious disease which in earlier days almost always led to chronic illness at best and early death at worst, his ultimate prospects of permanent recovery depend largely on other help which may be given him. Particularly they depend on the effect of rest treatment to build up his resistance for the long battle against the tubercle bacilli which survive in his tissues.

If resistance against infection has risen to a high level during treatment and the residuals of disease are small, the prognosis for permanent recovery is excellent. The recovery un-

der drug treatment of patients whose resistance is poor usually is followed sooner or later by relapse. However, surgical removal of the grossly damaged tissue, if practicable, may effectively turn the balance in such a patient's favor. Obviously, therefore, each case must be considered according to its individual features.

Certainly, a most important principle is to treat the patient with recently developed and limited tuberculosis promptly and sufficiently long to prevent extensive destruction of tissues and chronic disease and to insure the best prospect of permanent recovery. Many of these patients have no symptoms, and their disease is discovered in case-finding surveys or in other routine examinations. Although the rest cure alone has been effective in a great majority, the time required has been long, often a year or more. Now, although recovery may not be speeded greatly by drugs, their use when needed should help assure a permanent arrest of the disease almost uniformly; only a few of such patients will require surgery.

In the more advanced and active cases, reliance is now placed chiefly on the immediate and prolonged use of combined drug therapy to gain early control of the infection and to permit resolution of inflammatory changes. Mechanical procedures such as thoracoplasty and artificial pneumothorax are usually reserved for mechanical problems such as residual unhealed cavities in the lungs. Similarly, surgical resection is preferably reserved for the time when the disease has been brought under control and the remaining problem is the threat of relapse. During this time of waiting, it is to be hoped that the resistance of the patient may rise to a maximum level under treatment so that the permanence of his recovery may be improved or assured.

Another debatable question is the place of the so-called ambulatory treatment. If this could be shown to be adequate, the obvious advantages are that the huge cost of hospital care would be reduced, the patient's morale possibly would be improved, and the patient would not suffer the usual heavy social and economic losses. It is questionable whether these theoretical advantages can be achieved without paying the price of frequent relapse or of long chronic disease

leading to disability and eventually to death. Certainly, the matter should be approached objectively. Almost every conceivable treatment of tuberculosis has been applied in the past to the ambulatory patient. The early favorable response frequently is deceptive, and the opportunity to bring about a permanent recovery is easily lost.

Patients as Sources of Infection

Tuberculous patients with long-established chronic disease who circulate and act as sources of infection in the community represent a serious situation everywhere. As life is saved or prolonged by treatment, the death rate drops but the number of living patients continues to be high, and in fact, rises in some groups, particularly elderly men. Since many of these patients are destined for continuing chronic and eventually fatal disease, the problem of eliminating the source of infection short of the death of the patient must be considered. Giving drugs and thus drying up pulmonary cavities appeals to the imagination as a practical public health measure, and studies of this possibility are under way.

Here again, the only reasonable attitude is an objective one. Thus far, no combination of drugs has proved permanently adequate in preventing open cavitory lesions from discharging bacteria. Furthermore, when a dry cavity

again becomes wet and starts discharging and the patient again starts coughing, he may be spreading drug-resistant strains which, when they infect a previously uninfected person, may produce disease which will not be amenable to drug therapy. The hope would be to circumvent this by resorting to different series of drugs, but the practical feasibility of this course is at best open to debate.

Prospects for the Future

In view of our better understanding of the various modes of treatment and of the outlook for the discovery of new drugs, the future holds brightening prospects for the tuberculous patient. To indulge in the hope of eventually finding an absolute and final cure of the disease would be idle at this time. The methods of study and investigation promising to lead to further knowledge are well known, but the time they require is necessarily long. One thing is certain, though: Progress will be made in laboratories and clinics like those of the Henry Phipps Institute, and the scientists who will achieve that progress will be of the same sterling character as that group at the Phipps which has given it such an illustrious past. We place in their hands, and in those of similarly competent and devoted workers, the privilege and responsibility of coming to grips with the almost limitless problems that remain.

Institute for Federal Hospital Administrators

The seventh Inter-Agency Institute for Federal Hospital Administrators will be held at the Walter Reed Medical Center, Washington, D. C., from October 26 through November 13, 1953. Participating in the institute will be key hospital administrators of the Army, Navy, Air Force, Veterans' Administration, Public Health Service, and the Bureau of Indian Affairs.

Speakers from Government agencies, schools of public health, and university departments of hospital administration will lecture and hold discussion sessions. Individual hospital problems will be analyzed.